UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

April 19, 2000

MEMORANDUM

SUBJECT: **Chlorpyrifos-methyl**. Human Health Risk Assessment. Chemical Number 059102. DP Barcode D26505.

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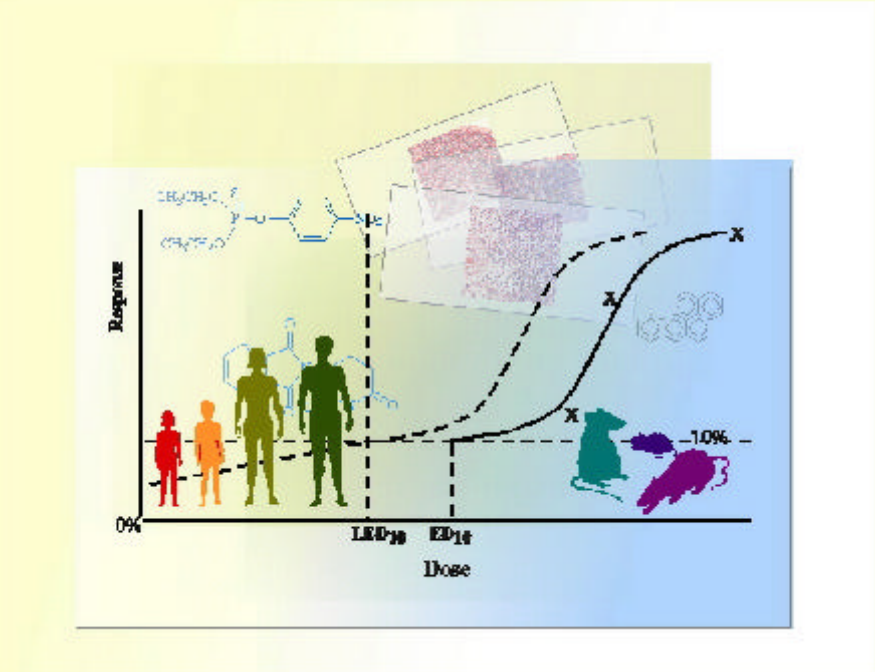
Attached please find a revised risk assessment for chlorpyrifos-methyl. Note that this document includes all changes due to the corrections and comments received and refinements in the dietary risk assessment.

HUMAN HEALTH RISK ASSESSMENT

Chlorpyrifos-Methyl



U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)

Gary Bangs, Risk Assessor
April 19, 2000

HUMAN HEALTH RISK ASSESSMENT

Chlorpyriphos-Methyl

Phase 5

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EXECUTIVE SUMMARY

The Health Effects Division (HED) has conducted a Preliminary Human Health Risk Assessment for the active ingredient chlorpyrifos-methyl for the purposes of making a Food Quality Protection Act (FQPA) tolerance reassessment for this post-1984 registered chemical. The toxicological database is not complete. Residue chemistry requirements are substantially complete pending receipt of limited confirmatory data.

Chlorpyrifos-methyl is an organophosphate insecticide used to protect stored grain, including wheat, barley, oats, rice, and sorghum. In addition to direct application to these grains, empty grain bins may also be treated. There are no other registered uses, hence no residential exposures to chlorpyrifos-methyl are anticipated. End-use product formulations consist of dusts and a liquid concentrate.

HAZARD ASSESSMENT

Adequate studies are not available to assess acute toxicity of chlorpyrifos-methyl. However, the available studies, conducted prior to the 1984 Subdivision F Guideline requirement, indicate chlorpyrifos-methyl to be of low to moderate toxicity via oral, dermal and ocular routes (Toxicity Category III). No technical studies for acute inhalation toxicity or dermal sensitization are available (although an acute inhalation toxicity study with the formulation product (43%) was submitted).

Chlorpyrifos-methyl is an organophosphate insecticide (O,O - dimethyl O-(3,5,6-trichloro-2-pyridyl)phosphorothioate) and its toxicity profile includes clinical signs and symptoms typical of other organophosphates that inhibit cholinesterase. Thus, inhibition of plasma, red blood cell (RBC), and/or brain cholinesterase was established as the critical endpoint for the risk assessment. Systemic toxicity included body weight loss, decreased food consumption, liver, kidney and adrenal pathology. The potential for chlorpyrifos-methyl to induce organophosphate induced delayed neurotoxicity (OPIDN) cannot be determined due to the lack of an acceptable acute delayed neurotoxicity study. A subchronic hen study did not indicate delayed type neuropathy in hens.

Neither the rat nor the mouse carcinogenicity studies showed evidence of carcinogenicity, and therefore the Hazard Identification Assessment Review Committee (HIARC) has classified chlorpyrifos-methyl as "not likely to be a human carcinogen." The mutagenicity database conforms to current standards and was noted to be positive only in an *in vitro* cytogenic assay in the presence of metabolic activation.

Developmental toxicity assessment is considered incomplete because only a prenatal developmental toxicity study in rats is available. The prenatal developmental toxicity study in a second species (rabbit) is unacceptable. Additionally, no multi generation reproductive toxicity study is available. Consequently, the HIARC, due to the inadequate toxicology database could not make a determination on the increased susceptibility to infants and children (as required by FQPA) from exposure to chlorpyrifos-methyl.

The FQPA Safety Factor Committee, following review of the hazard (toxicology) and exposure data, has determined that the 10x safety factor for increased susceptibility to infants and children should be retained. The inadequacy of the toxicology database precludes an evaluation of potential increased susceptibility of infants and children from exposure to chlorpyrifos-methyl (FQPA Safety Factor Recommendations for the Organophosphates dated August 6, 1998).

No dermal absorption studies are available for chlorpyrifos-methyl. Therefore, the HIARC extrapolated a dermal absorption factor by "bridging" data from oral and dermal studies conducted with chlorpyrifos[ethyl]. This comparison is considered reasonable due to the similarity of the physical characteristics affecting absorption for these two chemicals. For chlorpyrifos[ethyl], in the oral rat developmental neurotoxicity study (MRID Nos. 44556901, 44661001), the LOAEL was 0.3 mg/kg/day and in the 21-day dermal toxicity study in rats, the LOAEL was 10 mg/kg/day (MRID No. 40972801). In both studies, the endpoint was cholinesterase inhibition. The resulting estimated dermal absorption is 3% (oral LOAEL 0.3 mg/kg/day ÷dermal LOAEL 10x 100 = 3%). This absorption factor is supported by a human pharmacokinetic study with chlorpyrifos[ethyl] that showed 1-3% dermal absorption.

Two human studies with chlorpyrifos-methyl were considered by the HIARC, but were classified as unacceptable for technical reasons. It is current Agency policy that a regulatory decision cannot be made based on a human study until a formal decision has been made concerning the ethical aspects of such use. As this ethics decision regarding the use of toxicology studies employing human subjects has not yet been made, the Agency selected doses and endpoints to calculate dietary and non-dietary risk in the current assessment based solely on animal studies. The HIARC selected the maternal NOAEL of 1 mg/kg/day from the rat developmental toxicity study based on inhibition of red blood cell cholinesterase activity at the LOAEL of 12.5 mg/kg/day for acute dietary risk assessment. The NOAEL of 0.1 mg/kg/day from the combined rat chronic/carcinogenicity study based on inhibition of plasma cholinesterase activity at the LOAEL of 1mg/kg/day was selected for chronic dietary risk assessments. An uncertainty factor of 100 (10x for inter-species extrapolation and 10x for intra-species variation) was applied to the NOAELs to derive an acute Reference Dose of 0.01 mg/kg/day and a chronic Reference Dose of 0.001 mg/kg/day. Due to the lack of dermal and inhalation toxicity studies, oral values were selected for these risk assessments: 1 mg/kg/day for short-term dermal and inhalation exposure and 0.1 mg/kg/day for intermediate- and long-term dermal and inhalation exposure risk assessments. Since oral values were selected, appropriate absorption factors (3% for dermal and 100% for inhalation) were used for route-to-route extrapolation and risk assessments. A Margin of

Exposure (MOE) of 100 is adequate for both dermal and inhalation occupational exposure risk assessments. The FQPA safety factor is not applicable to occupational risk assessments. There are no registered residential uses at the present time.

Application of the 10x FQPA Safety Factor resulted in the acute Population Adjusted Dose (aPAD) of 0.001 mg/kg/day for acute dietary risk assessment and a chronic Population Adjusted Dose (cPAD) of 0.0001 mg/kg/day for chronic dietary risk assessment. The PAD is an acute or chronic RfD modified by the acute or chronic FQPA Safety Factor, respectively (RfD/FQPA Safety Factor = PAD).

According to a review of the OPP Incident Data System and national and California state poisoning registries, "relatively few incidents of illness have been reported due to chlorpyrifos-methyl." Chlorpyrifos-methyl was not in the top 200 chemicals reported to the National Pesticide Telephone Network in 1984-1991. Ten incidents of health effects that may have been associated with chlorpyrifos-methyl were reported to the Poison Control Centers, four of which were seen by a health care provider and one was hospitalized, but none with serious outcomes. There were no California poisoning registry incidents recorded for chlorpyrifos-methyl (1982-1995). There were insufficient data on which to base recommendations. (Attachment F, J. Blondell, Review of Chlorpyrifos Methyl Incident Reports, 4/15/99).

EXPOSURE AND RISK ESTIMATES

Four exposure and risk assessments were conducted for chlorpyrifos-methyl for the following exposure routes and durations: acute and chronic dietary, and occupational Short- and intermediate-term.

The Agency has updated the list of raw agricultural and processed commodities and feedstuffs derived from crops (OPTS 860.1000). As a result, additional chlorpyrifos-methyl residue data are now required for some commodities; these data requirements have been incorporated into this document and will be imposed upon its issuance but should not impinge on the FQPA reassessment decisions for chlorpyrifos-methyl. The need for revisions to dietary exposure/risk assessments will be determined upon receipt of the required residue chemistry data. Additional confirmatory data pertaining to storage stability remain outstanding (see attached Residue Chemistry Chapter for details).

DIETARY EXPOSURE AND RISK

Tier I and Tier II acute and chronic dietary risk concerns using the Dietary Exposure Evaluation Model (DEEM™) prompted HED to conduct a Tier III acute and chronic dietary risk analyses. The exposure estimates have been highly refined using anticipated residues based on USDA Pesticide Data Program (PDP) monitoring data for wheat and milk.

As part of the Dow Agro Sciences response (7/19/99, MRID 449069, D259302) to HED's preliminary risk assessment (G. Bangs, 9/20/99, D259632), the registrant stated that HED did not utilize all of the available processing data in the acute and chronic dietary analyses (S. Law, 6/8/99, D256070). New processing factors were calculated beyond those identified in the original review. If more than one processing study was conducted on the same raw agricultural commodity (RAC), then the average processing factor was calculated from the studies. Additionally, residue reduction factors obtained from cooking studies reported in the open literature were used in the assessment. The revised acute and chronic dietary exposure analyses incorporate: (1) additional processing factors from reevaluation of the processing data; (2) cooking factors obtained from the newly submitted open literature studies; and (3) recent policy changes concerning the treatment of blended and non blended food forms in the dietary analysis (HED SOP 99.6, 8/20/99).

Refined acute and chronic dietary exposure and risk estimates associated with the supported uses of chlorpyrifos-methyl **do not exceed HED's level of concern** for any population subgroup. HED's level of concern for acute and chronic dietary risk is 100% of the aPAD and cPAD, respectively. The results of the acute and chronic analyses indicate that the acute probabilistic and chronic dietary risk estimates associated with the proposed uses of chlorpyrifos-methyl are **below HED's level of concern** (< 100% aPAD; < 100% cPAD) for all population subgroups. However, it is significant that, although low, nearly all products analyzed that contained processed commodities derived from grains (flour, bran, etc.) Had measurable chlorpyrifos-methyl residues.

Because of the use pattern for chlorpyrifos-methyl (on stored grains and inside grain storage facilities), residues in water are not anticipated. Therefore, a drinking water exposure analysis was not conducted.

OCCUPATIONAL EXPOSURE AND RISK

Grain elevator workers are known to apply this product in liquid (1% ai dilute solution) or dust (2-3% ai) form to a moving stream of grain (i.e., conveyor or auger) using automated equipment. Only mixing and loading are expected to contribute significantly to worker exposure when using an automated process. Grain storage workers and farm workers also apply liquid chlorpyrifos-methyl to the walls of empty grain storage containers using hand sprayers, such as backpack or high-pressure hand wands. Dusts may be applied by hand or power-duster on top of grain in storage containers, or by mixing the product in with a shovel while the grain is still in the truck.

The baseline, short-term, combined dermal and inhalation risk for all of the available application scenarios except open loading of dust **did not exceed** HED's level of concern for chlorpyrifos-methyl (the MOEs are greater than 100 except for high pressure handwand, which is 93). The baseline, intermediate-term, combined dermal and inhalation MOEs for all available exposure scenarios except mixing/loading liquids **exceed** the Agency's level of concern. The combined intermediate-term MOEs for chlorpyrifos-methyl with maximum personal protective equipment (PPE) also **exceed** the Agency's level of concern, except for mixing and loading of liquid formulation (MOE 320). The combined dermal and inhalation risk estimates for all short-term exposure estimates using maximum PPE **do not exceed** HED's level of concern (MOEs are greater than 100). Several exposure scenarios (i.e., treating grain in truck or grain bin by hand or mechanical means with dust) have **no data** available. An attempt was made to characterize dermal short-term exposure to dusts based on published exposure studies of the application of dust to gardens. The MOEs calculated for the dust application scenario (dermal exposure only) **exceeded** the level of concern, with a maximum MOE of 21 with maximum PPE, even though it is expected that actual grain application exposures (dermal and inhalation) would be greater. U.S. Department of Agriculture grain inspectors and extension agents in several areas were contacted, and stated that hand application of dust is not widely practiced, but powered dusters, blowers, or automated systems are preferred. Additional data regarding occupational uses - duration, frequency, formulation use - have been requested via a meetings and conference calls with the USDA, the registrant, growers, and many other interested parties. These data would help to characterize worker exposure and the appropriate toxicological endpoint to use.

Post-application risks include bystander exposure to dusts generated by grain being conveyed into, out of or within storage containers, and dermal exposure when sampling treated grain. Personnel rarely have direct contact with the stored grain and therefore skin exposure is only a concern during short exposures such as testing of grain or maintenance work. The employees of a grain elevator or farmer/operator who operates a portable auger to load treated grain into a bin may be exposed to treated grain dust, but inadequate data are available to quantify such exposures. Therefore, chemical-specific data for handler and post-application exposure to insecticidal dust are required to complete the risk assessment.

As this product is only labeled and used for commercial grain storage, no residential exposures are anticipated. Label-required precautions for personal and general hygiene must be followed to prevent contamination of the work site or other areas (e.g., vehicles, residences). An aggregate risk estimate is not required, because drinking water and residential exposures to chlorpyrifos-methyl are not anticipated.

1 Hazard Assessment

1.1 Toxicology Assessment

The toxicology database for chlorpyrifos-methyl is incomplete. Currently there are data gaps for the following studies. Inclusion of the study as a data gap (see below) means that there is currently no acceptable study for the listed study type.

870.1100	Acute oral toxicity-Rat
870.1200	Acute dermal toxicity -Rabbit
870.1300	Acute inhalation study- Rat
870.2400	Primary ocular irritation-Rabbit
870.2500	Primary dermal irritation-Rabbit
870.2600	Dermal sensitization study- Guinea pigs
870.6100	Delayed neurotoxicity study - Hens
870.6200	Acute neurotoxicity study - Rat
870.3200	Subchronic dermal toxicity study - Rat or Rabbit
870.3465	Subchronic inhalation study -Rat
870.6200	Subchronic neurotoxicity study -Rat
870.4100	Chronic toxicity-Dog
870.3700	Prenatal developmental study - Rabbit
870.3800	Two-generation reproduction study - Rat
870.6300	Developmental neurotoxicity study -Rat
870.7485	General metabolism-Rat
870.7600	Dermal Absorption

Table 1. Acute Toxicity of Chlorpyrifos-methyl Technical

Guideline No. and Study Type	MRID #	Results	Toxicity Category
81-1 (870.1100) Acute Oral	242152*	LD_{50} = 2140 (1530-2990) mg/kg for males = 1090 (694-1710) mg/kg for females	III
81.2 (870.1200) Acute Dermal	242152*	LD_{50} > 2000 mg/kg.	III
81.3 (870.1300) Acute Inhalation		Data Gap	NA
81.4 (870.2400) Primary Ocular	242152*	Slight irritation in all eyes. Clearing 5/6 rabbits in seven days.	III
81.5 (870.2500) Primary Dermal	242152*	Irritation in 2/3 rabbits on days 4-7 exposure.	III

Guideline No. and Study Type	MRID #	Results	Toxicity Category
81.6 (870.2500) Sensitization	44906901 44989001	Delayed Contact Hypersensitization Study in the Guinea Pig [Unacceptable/ not upgradable]	NA
81.7 (870.6100) Neurotoxicity - hens	0029503	UNACCEPTABLE study	NA
81.8 (870.6200) Neurotoxicity screen - rats		Data Gap	NA

* Study conducted prior to the 1984 Subdivision F Guidelines
NA = Not applicable due to lack of data.

Chlorpyrifos-methyl is moderately toxic (Tox Category III) via the oral and dermal routes of exposure and is a slight eye and skin irritant. There is no technical study on dermal sensitization or acute inhalation toxicity. However, an acute inhalation toxicity study with the formulation product (43%) showed an LC_{50} of 4.8 mg/L in males and 5.2 mg/L in females (Tox category III). Hazard assessment is limited to the following acceptable toxicity studies.

1.1.1 Subchronic Toxicity

In a subchronic toxicity study (MRID 44906902, 45048301), primary groups of Fischer-344 rats (10/sex/dose) were administered chlorpyrifos-methyl (Reldan® F, 95.2% a.i.) in the diet at dose levels of 0 (control), 0.1, 1, 10 and 250 mg/kg/day for 13 weeks. Concurrent satellite groups, designated as recovery rats (10/sex/dose), were fed with either 0 or 250 mg/kg/day chlorpyrifos-methyl for 13 weeks and then allowed four weeks for recovery. For females, the NOAEL for plasma cholinesterase inhibition was 0.1 mg/kg/day and the LOAEL was 1.0 mg/kg/day. For males, a NOAEL was not established for plasma cholinesterase inhibition; the LOAEL was 0.1 mg/kg/day. The NOAEL for red blood cell and brain cholinesterase inhibition was 1.0 mg/kg/day and the LOAEL was 10 mg/kg/day in both sexes. The NOAEL for systemic toxicity was 1.0 mg/kg/day and the LOAEL was 10 mg/kg/day based on histopathology (hypertrophy, vacuolation and necrosis) of the adrenal.

1.1.2 Neurotoxicity

Chlorpyrifos-methyl did not induce OPIDN following repeated dose administration in hens. In a range-finding study (Accession No.: 072888), White Leghorn hens were given chlorpyrifos-methyl in corn oil at doses of 0, 50, 100, 250, 500, 750, or 1000 mg/kg/day, 5 days/week for four weeks. The high dose was subjected to histopathological evaluation of brain, spinal cord, and peripheral nerves. Slight to moderate ataxia and CNS depression accompanied by substantial weight loss were observed at 750 and 1000 mg/kg/day. At the 1000 mg/kg/day, 2/5 hens died.

No microscopic lesions indicative of delayed neurotoxicity were seen at 1000 mg/kg/day.

In a subchronic delayed neurotoxicity study (Accession No.: 0072888), chlorpyrifos-methyl in corn oil was administered by gavage at dose levels of 0, 5, 50 or 500 mg/kg/day, 5 days/week for a total of 65 doses to White Leghorn (nine months old) hens. No clinical signs of delayed neurotoxicity were seen at any dose level. A significant decrease in body weight as well a decrease in egg production was seen in hens at 500 mg/kg/day. At 500 mg/kg/day, the lesions reported were very slight axonal degeneration in one to four hens and very slight focal gliosis in one to six hens. Although there was no dose-response, the severity of the changes among treated hens was greater than those observed for the vehicle (corn oil) controls but less than those observed for the positive (TOCP) controls. They were similar in nature to the background neuropathological changes reported in the literature for white leghorn hens. There were no histopathological lesions indicative of delayed neurotoxicity in hens.

1.1.3 Developmental Toxicity

Pregnant Sprague-Dawley rats received oral administration of chlorpyrifos-methyl (96.9%) in corn oil at 0, 1, 12.5 or 50 mg/kg/day during gestation days 6 through 15. Post- dosing salivation in 10% of the dams at 50 mg/kg/day was the only clinical sign of treatment. There were no treatment-related effects on survival, maternal body weight, or food consumption. Plasma, red blood cell and brain cholinesterase was measured on Gestation Day 20 (i.e., five days after the last dose). Red blood cell cholinesterase inhibition was seen in dams at 12.5 mg/kg/day (33% $p<0.01$) and at 50 mg/kg/day (47%) dose groups. Plasma cholinesterase was inhibited – 8%, 8%, and 13% ($p < 0.01$) – at 1, 12.5 and 50 mg/kg/day, dose groups, respectively, with statistical significance only at the highest dose. Brain cholinesterase inhibition was seen only at the high dose ($p <0.01$). For maternal toxicity, the NOAEL was 1 mg/kg/day and the LOAEL was 12.5 mg/kg/day based on red blood cell cholinesterase inhibition. No developmental toxicity was seen; there were no treatment-related increases in external, visceral or skeletal malformations or anomalies. For developmental toxicity, the NOAEL was 50 mg/kg/day (HDT); a LOAEL was not established. The NOAEL of 1.0 mg/kg/day from this study was the dose selected for deriving the acute reference dose (RfD) as well as endpoints for short-term dermal and inhalation exposure risk assessments.

1.1.4 Carcinogenicity/Chronic Toxicity

Chlorpyrifos-methyl (95.2% a.i.) was administered to 60 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 0.05, 0.1, 1.0 and 50 mg/kg/day for 24 months. Ten rats/sex/dose were sacrificed at 53 weeks. Overt clinical signs of cholinesterase inhibition were not detected during the cageside observation periods. The high dose level male group showed a decrease in body weight gain of 12.8% and a statistically-significant decrease in absolute body weight of 7.6% compared to controls. In males, this decrease started at about day 68 and continued to the end of the study. In the females, the weight change at all dose levels versus the control was considered to be not toxicologically remarkable. No toxicologically-significant changes in the urinalysis, hematological or clinical parameters were observed in treated animals at any dose level. Cholinesterase in both sexes was statistically-significantly depressed at all time periods measured at the 1 mg/kg/day (plasma, 40-46% at 24 months) and 50 mg/kg/day (plasma, 85-94% at 24 months and brain, 37-47% at 24 months) dose levels versus the controls. RBC cholinesterase was sporadically depressed in both sexes at various time periods at 50 mg/kg/day.

At the terminal sacrifice, the adrenal cortex in the males showed a treatment-related increase in the incidence of slight/moderate degree of diffuse vacuolation reaching 100% incidence at 50 mg/kg/day. In females, increases in adrenal vacuolation were seen only at 50 mg/kg/day with an incidence of 98%. This vacuolation was consistent with lipid accumulation of the zona fasciculata and an increase in the absolute and relative adrenal weight. Statistically- significant increase in adenomas of the pars distalis in the pituitary were seen in the females but the effect did not appear to be dose-related. No other statistically-significant increases in tumor incidences versus control were seen. There was no evidence of carcinogenicity in male or female rats. Based on cholinesterase inhibition, the LOAEL is 1 mg/kg/day and the NOAEL is 0.1 mg/kg/day, which was used to derive the chronic reference dose.

In a carcinogenicity study, chlorpyrifos-methyl (97.4% a.i., lot no. AGR 219561) was administered to groups of a 52/sex pathogen free ICR Crj:CD-1® mice in the diet at concentrations of 0, 1, 5, 50, or 500 ppm for up to 78 weeks in the main study group. These concentrations resulted in a nominal compound intake for each concentration level of 0.0816, 0.418, 4.40, and 44.0 mg/kg/day for males and 0.0815, 0.403, 3.94, and 41.5 mg/kg/day for females for 1 ppm, 5 ppm, 50 ppm, and 500 ppm dietary mixtures, respectively. Satellite groups containing 44 mice per sex per group were fed the same diets for 26 and 52 weeks. Systemic treatment related effects were noted at 500 ppm only. The mean body weights of males were decreased by 12% at 52 weeks and 17% at 78 weeks. Food consumption was slightly decreased in males during the first 12 weeks of the study, and the overall food efficiency of males was

lower than the control group (control 1.2; 500 ppm, 1.0, NS). The total blood cholesterol was increased in males by 39% ($p < 0.05$) compared to the control at 26 weeks and in females by 45-79%, ($p < 0.05$ or 0.01) at all time points. Increased incidences of fatty changes in centrilobular hepatocytes were seen in males killed at 52 weeks (500 ppm, 75%; 25% of controls; $p < 0.01$), in main study males (500 ppm, 40%; controls, 18%, $p < 0.01$), in females killed at 52 weeks (500 ppm, 71%; controls 4%, $p < 0.01$), and in main study females (500 ppm, 40%; controls, 6%, $p < 0.01$). The incidence of diffuse hepatocellular fatty change was statistically increased in main study females *only* at 50 ppm (50 ppm 15%; control 2%, $p < 0.05$) and was marginally ($p = 0.07$) increased at 5 ppm. A significantly increased incidence of kidney tubular atrophy was seen in main study males (500 ppm, 60%; controls 34%, $p < 0.01$). The incidence of kidney tubular atrophy was marginally but not statistically-significantly increased at 50 ppm ($p = 0.08$) in main study males. Swelling of adrenal cortical cells occurred in 42% ($p<0.01$) of main study and 25% ($p < 0.01$) of 52-week interim sacrifice male mice but did not occur in any animals fed the lower doses or the control groups. The LOAEL for systemic effects is 500 ppm for both sexes (44.0 mg/kg/day for males and 41.5 mg/kg/day for females) based on histopathologic lesions in the liver, kidney, and adrenal glands. The NOAEL is 50 ppm (4.40 mg/kg/day for males and 3.94 mg/kg/day for females).

Cholinesterase from plasma and red blood cells was moderately inhibited at 50 ppm by 47-70% ($p < 0.01$ or < 0.05) in males and by 31-75% ($p < 0.01$ or < 0.05) in females and severely inhibited at 500 ppm by 93-96% ($p < 0.01$) in males and by 87-97% ($p < 0.01$) in females at all time points (26, 52, and 78 weeks). Brain cholinesterase was significantly decreased by 53-64% ($p < 0.01$) in 500-ppm group males and by 45-50% ($p < 0.01$) in 500-ppm group females at all time points. At 50 ppm, brain cholinesterase was statistically decreased in males (14%, $p < 0.05$) only at week 78, and in females a statistical decrease (25%, $p < 0.01$) was seen only at week 52. The LOAEL for inhibition of cholinesterase is 50 ppm for both sexes (4.40 mg/kg/day for males and 3.94 mg/kg/day for females). The NOAEL is 5 ppm (0.418 mg/kg/day for males and 0.403 mg/kg/day for females). Treatment for up to 78 weeks with chlorpyrifos-methyl did not result in a significant increase in the incidence of neoplastic lesions at any site. The animals were adequately dosed as evidenced by decreased cholinesterase at 50 ppm and treatment-related microscopic lesions in both sexes at 500 ppm. There was no evidence of carcinogenicity in male or female mice.

The acceptable mutagenicity studies are tabulated below.

Table 2. Mutagenicity Studies

Study Type	Comments
Bacterial Mutagenicity (Ames test). MRID No.: 41887601.	No evidence of mutagenic effects ± metabolic activation (S9) at dose levels up to 10,000 Fg/plate.
In vitro cytogenetic assay in CHO cells. MRID No.: 00154130.	-No evidence of a clastogenic effect in the absence of metabolic activation 4 to 40 Fg/mL. -In the presence of metabolic activation (S9) and at 15 and 50 Fg/mL chlorpyrifos-methyl was determined to be positive clastogenic *in vitro*.
In vitro gene mutations in the CHO/HGPRT. MRID No.: 00146053. (1985 study).	-No evidence of mutagenic effects ± metabolic activation (S9).
In vivo mouse micronucleus assay. MRID No.: 00145108.	-No evidence of clastogenic effects at dose levels up to 1460 mg/kg.
In vitro unscheduled DNA synthesis in rat primary hepatocytes.	-No evidence of genotoxic response at dose levels up to 32.26 Fg/mL.

1.1.5 Human Data

It is current Agency policy that a regulatory decision cannot be made based on a human study until a formal decision has been made concerning the ethical aspects of such use. As this ethics decision regarding the use of toxicology studies employing human subjects has not yet been made, the Agency selected doses and endpoints to calculate dietary and non-dietary risk in the current assessment based solely on animal studies. HED has previously determined that both of these studies are unacceptable for use in risk assessments.

The Chmiel *et al.*, (MRID 00030755, 00043239) study, conducted at IBT in 1975, was reviewed by HED and was classified as Invalid due to numerous technical deficiencies (HED Document No. 001571). The study did not report data on clinical symptoms, physical examination, post- treatment values for hematology, clinical chemistry, and urinalysis. The study was conducted without medical supervision and there was no evidence of voluntary consent by the subjects.

The Coulson *et al.*, 1975 (MRID 00030754, 00043238) study was reviewed by the HIARC on January 14, 1999. The HIARC determined this study to be unacceptable for use in risk assessments due to lack of test article characterization. The study report did not provide data on purity, batch/lot number, or a physical description of the test material. The HIARC further determined that this study was not appropriate for use in risk assessment due to technical limitations such as: only a small number of subjects (5) were used; only one sex (males; no females) was used; the health status of the subjects and the confounding factors (e.g., smoking, alcohol consumption, etc.) were unknown; and the study has limited statistical power of detection.

1.2 Dose Response Assessment

1.2.1 Determination of Susceptibility

The Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database and concluded that:

(1) The toxicology database is incomplete.

(2) There are unacceptable studies for acute delayed neurotoxicity in hens (series 81-7), developmental toxicity in rabbits (83-3) and reproductive toxicity in the rat (83-4). There are data gaps for acute (series 81-8) or subchronic (series 82-7) neurotoxicity screen studies in rats. The developmental neurotoxicity study is considered a data gap until completion of the data gaps for the series 81-7, 81-8, 82-7, 83-3 (rabbit) and 83-4 studies at which time the need for this study will be reevaluated.

(3) It could not make a determination on the increased susceptibility to infants and children (as required by FQPA) to chlorpyrifos-methyl due to the inadequate toxicology database (Attachment A. Toxicology Endpoint Selection - Report of the Hazard Identification Assessment Review Committee, 5/17/99).

The FQPA Safety Factor Committee, following review of the hazard and exposure data, determined that the 10x safety factor for increased susceptibility to infants and children should be retained. The inadequacy of the toxicology database precludes an evaluation of potential increased susceptibility of infants and children from exposure to chlorpyrifos-methyl (Attachment B. FQPA Safety Factor Recommendations for the Organophosphates, 8/6/98).

1.2.2 Toxicology Endpoint Selection

The toxicology endpoints selected for dietary and non-dietary risk assessments are presented in Table 3.

Table 3. Toxicology Endpoints Selected for Risk Assessments

Exposure Scenario	Dose (Mg/kg/day)	Endpoint	Study
Acute Dietary General Population Including Infants and Children	NOAEL= 1 mg/kg/day	Inhibition of red blood cell cholinesterase at 12.5 mg/kg	Rat developmental toxicity (MRID No.: 44680603)
	UF = 100 FQPA = 10	**Acute RfD = 0.01 mg/kg** **Acute PAD = 0.001 mg/kg**	
Chronic Dietary	NOAEL= 0.1 mg/kg/day	Inhibition of plasma cholinesterase at 1 mg/kg/day	Chronic/Carcinogenicity feeding study in rats (No.: 42269001)
	UF = 100	**Chronic RfD = 0.001 mg/kg/day** **Chronic PAD = 0.0001 mg/kg/day**	
Dermal Absorption	3% based on comparison of the oral and dermal toxicity studies with chlorpyrifos[ethyl] using a common species and endpoint.[1]		
Short-Term (Dermal/ Inhalation)	Oral NOAEL= 1 mg/kg/day	Inhibition of red blood cell cholinesterase at 12.5 mg/kg/day. (Dermal absorption of 3% and inhalation absorption equivalent to oral, i.e., 100% of oral)	See Acute Dietary
Intermediate-Term (Dermal/ Inhalation)	Oral NOAEL = 0.1 mg/kg/day	Inhibition of plasma cholinesterase noted at the 90-day measurement at 1 mg/kg/day. (Dermal absorption of 3% and inhalation absorption equivalent to oral, i.e., 100% of oral)	See Chronic Dietary
Long Term (Dermal/ Inhalation)	Oral NOAEL = 0.1 Mg/kg/day	Inhibition of plasma cholinesterase at 1mg/kg/day (Dermal absorption of 3% and inhalation absorption equivalent to oral, i.e., 100% of oral)	Chronic/Carcinogenicity feeding study in rats (No.: 42269001)
Carcinogenicity	Classified as "not likely a human carcinogen."		

PAD = Population Adjusted Dose

[1]This absorption factor is supported by a human pharmacokinetic study with chlorpyrifos[ethyl].

2 Exposure Assessment

2.1 Registered Uses

Chlorpyrifos-methyl [*O,O*-dimethyl-*O*-(3,5,6-trichloro-2-pyridyl)phosphorothioate] is an insecticide registered for use on stored grain crops including barley, oats, rice, sorghum, and wheat. Chlorpyrifos-methyl is manufactured by Dow under the trade name Reldan®. Chlorpyrifos-methyl formulations registered to DowElanco for use on food/feed crops include the technical grade and one emulsifiable concentrate (EC) formulation (another registrant, Gustafson, also has two registered dust formulations). Application of this product is limited to post- harvest treatment of stored grains or grain storage facilities.

2.2 Dietary Exposure

The qualitative nature of the residue in plants is adequately understood based on metabolism studies conducted on stored corn and wheat grain. HED had previously determined that 3,5,6-trichloro-2-pyridinol (TCP) is no longer a residue of concern with respect to chlorpyrifos because of its inactivity as a cholinesterase inhibitor (E. Doyle, 4/1/91). Therefore, HED concluded that TCP need not appear in the tolerance expression, and that tolerances are to be expressed in terms of chlorpyrifos-methyl *per se* (M. Flood, 4/29/91). The qualitative nature of chlorpyrifos-methyl residues in animals is adequately understood based upon acceptable ruminant and poultry metabolism studies. HED has determined that the residue to be regulated in animal commodities is chlorpyrifos-methyl *per se*.

The Pesticide Analytical Manual (PAM) Vol. II lists a GC/ECD method (Method I) that determines the combined residues of chlorpyrifos-methyl and TCP in or on stored grain commodities following conversion of chlorpyrifos-methyl to TCP *via* hydrolysis; residues of TCP are then derivatized prior to GC analysis. This method is not ideal for enforcement purposes because it is not capable of specifically determining residues of chlorpyrifos-methyl *per se*; combined residues of chlorpyrifos-methyl and TCP are measured. However, adequate methodology is available to enforce tolerances for residues in/on plant commodities: The FDA PESTDATA database (PAM Vol. I, January 1994) indicates that chlorpyrifos-methyl is completely recovered using FDA Multiresidue Protocols D and E (PAM I Sections 232.4 and 211.1). Residue data on stored grains and grain processed commodities were collected using adequate analytical methods (Methods ACR 78.18 and ACR 77.6(3), respectively) capable of determining chlorpyrifos-methyl *per se*. The registrant should conduct an independent laboratory validation (ILV) for one of these methods and submit results to the Agency. The Agency will then conduct a tolerance method validation (TMV). The GC/FPD method listed in PAM Vol. II (Method II) capable of determining residues of chlorpyrifos-methyl *per se* in meat, milk, and eggs of livestock is adequate for enforcement of tolerances on animal commodities.

The Agency previously concluded that residues on stored corn grain could not practically be controlled by use label restrictions because stored grain can be moved from one location to another and treated at each location (DP Barcode D169228, J. Morales, 4/30/92). To address the potential for over-tolerance residues resulting from multiple post- harvest grain treatments using chlorpyrifos-methyl, Gustafson, Inc., a registrant, has developed an immunoassay procedure to be used in grain storage areas to verify that grain has not been previously treated. The method, which can rapidly detect residues in excess of 0.1 ppm, was independently validated (DP Barcode D193346, M. Flood, 3/10/94) and has been successfully validated by the Agency's Analytical Chemistry Branch (DP Barcode D200683, M. Flood, 6/15/94). This method cannot be substituted for the Agency-validated, conventional analytical method required for enforcement purposes, but is suitable for pre-treatment testing.

Adequate storage stability data are available for the purposes of risk assessment. Although no storage stability data were submitted to support the residue studies, the existing storage stability data for chlorpyrifos suggest that residues of chlorpyrifos-methyl are stable frozen in stored plant and animal matrices. Storage stability data on chlorpyrifos-methyl are needed to confirm these assumptions. Samples should be held in frozen storage for time periods equal to those in the magnitude of the residue study and then analyzed for chlorpyrifos-methyl.

Residue data are available from a study in which samples of barley, corn, oat, rice, sorghum, and wheat grain were treated with chlorpyrifos-methyl once at 6 ppm (1x rate) and analyzed for residues of chlorpyrifos-methyl immediately following treatment and after storage intervals of 0 (up to 50 days post- treatment), 1, 3, 6, and 12 months. Residues of chlorpyrifos-methyl *per se* were 4.3-7.0 ppm in/on one sample each of barley (5.4 ppm), corn (4.3 ppm), oats (5.2 ppm), rice (7.0 ppm), and wheat (5.5 ppm) grain analyzed immediately after treatment. [HED notes that the rice residue value of 7.0 ppm must have resulted from an application greater than 1x; therefore, the rice highest average field trial (HAFT) that will be used is 6.0 ppm.]

Data are needed from three studies depicting residues of chlorpyrifos-methyl in/on treated wheat grain stored in chlorpyrifos-methyl-treated storage facilities and sampled on the day of treatment following applications at the maximum use rate. The trials should include the use of both water and mineral oil as the spray diluent. The current labels allow treatment of storage facilities prior to storage of treated grain, and data reflecting this potential "worst-case" scenario were not provided by the original residue studies.

Pending resolution of storage stability issues, the reassessment requirements for magnitude of chlorpyrifos-methyl residues in processed food/feed commodities are fulfilled for stored grain commodities. Currently, tolerances are established for the combined residues of chlorpyrifos-methyl and TCP in milled fractions (exc. flour) of barley, oats, rice, sorghum, and wheat at 30-120 ppm. These tolerances were determined based on the proposed tolerances for the grain (6.0 ppm) and the highest concentration factor found for the combined residues in any processed grain fraction. In the following reassessment, tolerances were determined using the concentration factor for residues in each regulated processed commodity and the HAFT residues for the specified grain (6.0 ppm).

Data from the corn processing study indicate that chlorpyrifos-methyl residues in/on corn aspirated grain fractions are 84 times higher than in/on corn grain (PP#6F3429, DP Barcode D169228, J Morales, 4/30/92). Data depicting the potential for concentration of chlorpyrifos-methyl residues in/on aspirated grain fractions derived from sorghum and wheat are required.

2.2.1 Anticipated Residues

The dietary exposure estimates for chlorpyrifos-methyl have been highly refined in that anticipated residues were used for all commodities included in the exposure analyses. Processing factors were also applied to the processed fractions of raw agricultural commodities.

Refinements such as anticipated residues (ARs) are a way to estimate actual exposures, as opposed to high-end estimates (i.e., tolerances). Monitoring data from the USDA Pesticide Data Program (PDP) are available to estimate ARs. Out of 1,562 monitoring data samples from PDP (1995-1997) for wheat, 920 samples (61%) had detectable residues; see **Table 4** for details. The wheat PDP residue values have been translated to the other supported raw agricultural commodities (RACs: barley, oats, rice and sorghum) because the use pattern of chlorpyrifos-methyl is the same. Processing factors, determined from processing studies, were also incorporated into the exposure analysis.

PDP monitoring data are also available for milk. Out of 1,297 monitoring data samples from PDP (1996-1997) for milk, none had detectable residues; see **Table 5** for details.

In general, the FDA Surveillance Monitoring data (1992-1998) supported the percentage of detections found in wheat by PDP. When choosing which data set to use for a probabilistic assessment, the order of preference is generally PDP data > FDA data > field trial data. Monitoring data (FDA or PDP) is preferred to field trial data because they are sampled longer after harvest and is therefore more reflective of residues consumed "at the dinner plate;" PDP data are preferred to FDA monitoring data because of the statistical design of the PDP program specific for dietary risk assessment and because the foods are prepared before analysis as they would be at home (i.e., peeling, washing, etc.). All monitoring data can be "decomposited" prior to use in acute dietary risk assessment; however, this is not necessary for chlorpyrifos-methyl because the raw agricultural and processed commodities on which it is used are considered “blended” commodities.

Table 4. Summary of Wheat PDP Data

Crop	Year	# of Samples Analyzed	# of Detects	% of Detects	Minimum Detectable Concentration (ppm)	Maximum Detectable Concentration (ppm)	Average Detectable Residues (ppm)	LOD (ppm)
Wheat	1995	600	325	54	0.002	3.322	0.11	0.001
Wheat	1996	340	249	73	0.002	1.525	0.09	0.001
Wheat grain	1997	622	346	56	0.002	1.796	0.11	0.001
Total		1562	920	Avg. = 61%				

Table 5. Summary of Milk PDP Data

Crop	Year	# of Samples Analyzed	# of Detects	% of Detects	Minimum Concentration Detected (ppm)	Maximum Concentration Detected (ppm)	Average of Detectable Residues (ppm)	LOD Range (ppm)
Milk	1996	570	0	0	ND	ND	ND	0.001-0.002
Milk	1997	727	0	0	ND	ND	ND	0.001-0.002
Total		1297	0	0				

For the purposes of dietary risk assessment, acute and chronic ARs based on monitoring data for chlorpyrifos-methyl have been calculated for barley, oats, rice, sorghum, grain, meat, milk, poultry and eggs; see summary Table 6.

Table 6. Acute and Chronic ARs for Dietary Risk Assessment

Commodity	Acute AR [2] (ppm)	Chronic AR [3] (ppm)
Barley, grain	0.06	0.06
Oats, grain	0.06	0.06
Rice, grain	0.06	0.06
Sorghum, grain	0.06	0.06
Wheat, grain	0.06	0.06
Fat of cattle, goats, horses and sheep	0.008	0.008
Meat of cattle, goats, horses and sheep	0.0001	0.0001
Liver of cattle, goats, horses and sheep	0.0001	0.0001
Kidney of cattle, goats, horses and sheep	0.0004	0.0004
Hogs, fat	0.007	0.007
Hogs, muscle	0.001	0.001
Hogs, meat by products	0.00009	0.00009
Milk	0.0008	0.0008
Milk, fat [4]	0.009	0.009
Poultry, fat	0.00004	0.00004
Poultry, meat	0.000005	0.000005
Poultry, liver	0.000005	0.000005
Eggs	0.00001	0.00001

[1] Acute and chronic ARs (RACs and meat, poultry and eggs) for dietary risk assessment from chlorpyrifos-methyl Residue Chemistry Chapter (S. Law, 6/8/99, D256666).

[2] The acute dietary risk assessment utilized the entire distribution of monitoring data (PDP) for the RAC incorporating ½ the LOD (for treated non-detects) to calculate the average residue (the PDP LOD = 0.001 ppm for all 3 years). For the acute milk AR, the monitoring data (PDP) was incorporated into a RDF (all non-detectable residues, therefore ½ the average LODs were used [range= 0.001-0.002 ppm]). For the meat, poultry and egg ARs, the AR was incorporated into an RDF. No further adjustment was made for meat, milk, poultry or egg %CT.

[3] The chronic dietary risk assessment utilized the monitoring data (PDP) for the RAC incorporating ½ the LOD (for treated non-detects) to calculate the average residue (the PDP LOD = 0.001 ppm for all 3 years). The chronic milk AR given here is the average residue values from the 1996-97 PDP data (all non-detectable residues, therefore ½ the average LOD was used [range= 0.001-0.002 ppm]). No further adjustment was made for meat, milk, poultry or egg %CT.

[4] The milk fat acute and chronic AR was re-evaluated since the chlorpyrifos-methyl Residue Chemistry Chapter (S. Law, 6/8/99, D256666). Upon re-evaluation, it was noted that chlorpyrifos-methyl residues concentrate by 13 X in milk, cream. Therefore, the milk AR (0.0008 ppm) was adjusted to reflect the 13 fold concentration in milk, cream (0.009 ppm).

2.2.2 Processing Studies

As part of the Dow Agro Sciences response (7/19/99, MRID 449069, D259302) to HED's preliminary risk assessment (G. Bangs, 9/20/99, D259632), the registrant stated that HED did not utilize all of the available processing data in the acute and chronic dietary analyses (S. Law, 6/8/99, D256070). Although the processing data were previously reviewed by HED (R. Perfetti, 3/13/81), new processing factors were calculated beyond those identified in the original review (Table 6). If more than one processing study was conducted on the same RAC, then the average processing factor was calculated from the studies. The calculated processing factors used for the specific DEEM™ food forms in these dietary assessments are discussed below. DEEM™ default processing factors were utilized in both the acute and chronic analyses for dried meat.

Additionally, residue reduction factors obtained from cooking studies reported in the open literature (Cogburn, *et al.*, "Fate of Malathion and Chlorpyrifos-Methyl in Rough Rice and Milling Fractions Before and After Parboiling and Cooking," *Journal of Economic Entomology*, **83 (4)**: 1636-1639, 1990. and Nakamura, *et al.*, "Reductions in Postharvest-Applied Dichlorvos, Chlorpyrifos-methyl, Malathion, Fenitrothion, and Bromide in Rice during Storage and Cooking Processes," *J. Agricultural and Food Chemistry*, **41**: 1910-1915, 1993) were incorporated into the dietary exposure analysis (Table 7). A residue reduction factor of 0.026X was calculated for boiled commodities; a residue reduction factor of 0.36X was calculated for baked/fried commodities. These reduction factors were applied to all of the RAC boiled and baked/fried food forms.

Table 7. Processing/Cooking Data

Reference	Crop	Application Rate (ppm)	Processed Fraction	Residue Detected (ppm)	Processing Factor
Cogburn *et al.*	Rice	6	Rough rice	4.45	
			Hulls	14.9	3.3
			Brown rice	0.87	0.2
			Bran	6.1	1.4
			Milled rice	0.14	0.03
			Cooked	0.06	0.013
Nakamura *et al.*	Rice	Intended Use (from polished rice)		% Remaining	
			Polished rice	100*	
		Boiled rice	Washed rice	18	0.018
			Boiled rice	3.8	0.038
			Polished rice	100*	
		Noodles	Washed rice	16.7	0.17
			Rice powder	16.7	0.17
			Raw noodle	3.1	0.031
			Steamed noodle	2.1	0.021
			Rice noodle	<1	<0.01

*Chlorpyrifos-methyl applied directly to the polished rice.

2.2.3 Acute and Chronic Dietary Exposure and Risk Estimates

HED's level of concern for acute and chronic dietary risk is 100% of the aPAD and cPAD, respectively. The results of the acute and chronic analyses indicate that the acute probabilistic and chronic dietary risk estimates associated with the proposed uses of chlorpyrifos-methyl are **below HED's level of concern** (< 100% aPAD; < 100% cPAD) for all population subgroups.

The complete lists of acute and chronic dietary exposures for all subpopulations are presented in the attached Dietary Exposure Analysis.

Subgroups in Tables 8 and 9 represent the dietary exposure for the U.S. population and the population subgroups higher than the U.S. population exposure.

Table 8. Acute Probabilistic Dietary Exposure Results for Chlorpyrifos-methyl

Subgroups	95th Percentile Exposure (% aPAD)	99th Percentile Exposure (% aPAD)	99.9th Percentile Exposure (% aPAD)
U.S. Population	0.000056 (6 %)	0.000096 (10 %)	0.000191 (19 %)
All infants (< 1 year)	0.000079 (8 %)	0.000147 (15 %)	0.000213 (21 %)
Non- nursing infants (< 1 year old)	0.000096 (10 %)	0.000159 (16 %)	0.000224 (22 %)
Children (1-6 years old)	0.000104 (10 %)	0.000163 (16 %)	0.000295 (30 %)
Females (13-19 years old/not pregnant/not nursing)	0.000037 (4 %)	0.000067 (7 %)	0.000199 (20 %)

Table 9. Chronic Dietary Exposure and Risk Estimates for Chlorpyrifos-methyl

Subgroups	Chronic Total Exposure (mg/kg/day)	Chronic Risk (% cPAD)
U.S. Population	0.000019	19 %
Non- nursing infants (< 1 year old)	0.000022	22 %
Children (1-6 years old)	0.000052	52 %
Children (7-12 years old)	0.000031	31 %
Females (13+ years old, nursing)	0.000024	24 %
Males (13-19 years old)	0.000020	20 %

2.2.4 Drinking Water Exposure

Because of the use pattern for chlorpyrifos-methyl (on stored grains and inside grain storage facilities), residues in water are not anticipated. Therefore, a drinking water exposure analysis was not conducted.

2.3 Incident Data

According to a review of the OPP Incident Data System and national and California state poisoning registries, "relatively few incidents of illness have been reported due to chlorpyrifos-methyl."[5] Chlorpyrifos-methyl was not in the top 200 chemicals reported to the National Pesticide Telephone Network in 1984-1991. Ten incidents of health effects that may have been associated with chlorpyrifos-methyl were reported to the Poison Control Centers, four of which were seen by a health care provider and one was hospitalized, but none with serious outcomes. There were no California poisoning registry incidents recorded for chlorpyrifos-methyl (1982-1995), and insufficient data on which to base recommendations.

2.4 Occupational Exposure and Risk

Based on the chlorpyrifos-methyl pattern of use, several exposure scenarios are plausible as defined by the types of application equipment and procedures that might be employed by chlorpyrifos-methyl handlers. Only 5% of the annual usage of a.i. (based on Quantitative Usage Analysis dated 4/19/98 by BEAD) is for treatment of empty grain storage bins, and approximately 95% is for grain protection. Handlers are potentially exposed to chlorpyrifos-methyl by mixing and loading 2-3% dust or 1% (diluted) liquid formulations for automated grain treatment (admixture), treating empty grain bins using high-pressure hand wand or backpack sprayer, or treating grain by hand or power dusting (top-dressing).

2.4.1 Application Rates

Mixer/loaders were assumed to handle up to 800 lbs. of 3% dust (24 lb.ai) or mix as much as 400 gallons of dilute liquid (29 lb. ai) for automated grain treatment, or 40 gallons (3.3 lb. ai) diluted for bin treatment per day. Mixer/loader/applicators were assumed to handle up to 100 lbs.of 3% dust (3 lb. ai) in turning-in grain treatment or 0.66 lb. ai top-dressing grain inside bins per day. Mixing, loading, and spraying empty bins with a backpack or high-pressure hand wand is estimated to expose handlers to 24 to 40 gallons (2-3.3 lb.ai) diluted product per day. These rates are based upon agricultural extension agents' best estimates, and are consistent with the physical sizes of grain collection and storage containers.

2.4.2 Application Scenarios

Only short- and intermediate-term exposures are anticipated for handlers of this chemical. Typical exposure for farmers is anticipated to be less than seven days per year (short-term), but for grain storage facility workers, more than seven but less than 180 days per year (intermediate-term). Treatment of grain with insecticide usually occurs immediately post-harvest as the grain is being stored or shortly after storage, if the grain will be stored rather than sold. This is expected to be a seasonal, intermittent activity, performed by certified farmers or storage facility workers themselves. Grain elevator workers are known to apply this product in liquid or dust form to a moving stream of grain (i.e., conveyor or auger) using automated equipment. Only mixing and loading are expected to contribute significantly to worker exposure when using an automated process. Grain storage workers and farm workers also apply liquid chlorpyrifos-methyl to the walls of empty grain storage containers using hand sprayers, such as backpack or high-pressure hand wands. Dusts may be applied by hand or power-duster on top of grain in storage containers, or by mixing the product in with a shovel while the grain is still in the truck.

2.4.3 Occupational Risk Estimates

A summary of exposure estimates and risk assessments for occupational handlers is included as Tables 10-12. There were no chemical-specific exposure data available for this chemical. Therefore, the risk assessment has been performed using surrogate data from the Pesticide Handler's Exposure Database (PHED, v. 1.1), where available. No data, surrogate or otherwise, were available for several pesticide handler scenarios (all dust applications). Therefore, chemical-specific data for handler and post-application exposure to insecticidal dust are required to complete the risk assessment. An attempt was made to estimate dust exposure based upon a study of residential insecticide use reported in the literature. Actual dust exposures in the occupational setting are expected to be higher, especially when standing in grain and mixing in product with a shovel.

Loader and applicator exposure were evaluated based on wearing long-sleeved shirt, long pants, chemical-resistant gloves, and shoes with socks; separate estimates were made with minimum label-required personal protective equipment and with maximum personal protective equipment. All of the Reldan® labels require *only* rubber gloves and eye protection.

The baseline, short-term, combined dermal and inhalation risk for all of the available application scenarios except open loading of dust **did not exceed HED's level of concern** (the MOEs are more than 100 except high pressure handwand, which is 93) for chlorpyrifos-methyl. The baseline, intermediate-term, combined dermal and inhalation MOEs for all available exposure scenarios except mixing/loading liquids **exceed the Agency's level of concern**. The combined intermediate-term MOEs for chlorpyrifos-methyl with maximum PPE also **exceed the Agency's level of concern**, except for mixing and loading of liquid formulation (MOE 320). The combined dermal and inhalation risk estimates for all short-term exposure estimates using maximum PPE **do not exceed HED's level of concern** (MOEs are greater than 100), except for dust application scenarios. No data are available for engineering control solutions for the scenarios that exceeded the level of concern, particularly dust formulations. An engineering control is not needed for liquid mixing and loading, and no known feasible engineering controls exist for hand application of sprays or dusts. Several exposure scenarios (i.e., treating grain in truck or grain bin by hand or mechanical means with dust) have no surrogate or chemical-specific data available. An attempt was made to characterize dermal short-term exposure to dusts based on published exposure studies of the application of dust to gardens. The MOEs calculated for the dust application scenario (dermal exposure only) **exceeded the Agency level of concern**, with a maximum MOE of 21 with PPE, even though it is anticipated that actual grain application exposures (dermal plus inhalation) would be greater.

2.5 Post-Application Exposure

Post-application risks include bystander exposure to dusts generated by grain being conveyed into, out of or within storage containers, and dermal exposure when sampling treated grain. Personnel rarely have direct contact with the stored grain and therefore skin exposure is only a concern during short exposures for testing of grain, maintenance, or other intermittent activities. Bystander dust exposure may be significant for either the employee of a grain elevator or farmer/operator who operates a portable auger to load treated grain into a bin. Label-required precautions for hygiene and laundry should be followed to prevent contamination of the work site or workers' residence.

2.6 Residential Exposure

Because of the use pattern for chlorpyrifos-methyl (on stored grains and inside grain storage facilities), residential exposures are not anticipated.

Table 10. Occupational Handler Short- and Intermediate-Term Exposure Estimate and Risk Assessment Summary for Chlorpyrifos-methyl : Baseline

		DERMAL					INHALATION					Combined MOE	
		(With minimum PPE)[a]					(With no respirator)					Min. PPE	
Application Scenario	(lb ai/ day)*	UE[b] (mg/lb ai)	ADD[c] (mg/kg/day)		ST MOE[d] NOAEL = 1 mg/kg	Int. MOE[d] NOAEL = 0.1 mg/kg	UE[e] (mg/lb ai)	ADD[f] (mg/kg/day)		ST MOE[d] NOAEL= 1 mg/kg	Int. MOE[d] NOAEL = 0.1 mg/kg	MOE Total[g]	
			Short-term	Inter. term				Short-term	Inter.-term			Short Term	Inter. Term
Mixer/Loader													
Open Loading Dusts [Wettable Powder] for Automated Application Systems (1)	24	0.17	2.0 E-3	1.8 E-3	500	56	0.0434	0.017	0.015	59	6.7	53	6.0
Mixing/Loading Liquids for Automated Application (2)	29	0.023	3.3 E-4	2.9 E-4	3000	340	0.0012	5.8 E-4	5.0 E-4	1700	200	1000	130
Mixer/Loader/Applicator													
3a)Treating Grain in Truck or (b)Top-Dressing Grain with Dust by Hand-Pump	3	200	0.30	0.26	3.3	0.39	No Data						
	0.66		0.066	0.057	15	1.8							
4a)Treating Grain in Truck or b) Top-Dressing Grain with Dust by Power Duster	No Data												
Backpack Spraying (5)	2	2.5	2.5 E-3	2.1 E-3	400	48	0.03	1.0 E-3	8.6 E-4	1000	120	290	34
High Pressure Handwand Sprayer (6)	3.3	2.5	4.1 E-3	3.5 E-3	240	28	0.12	6.6 E-3	5.7 E-3	150	18	93	11

[*] There are 2 strengths of dust, but the 3% was selected for calculations as they will be more conservative and thus suffice for 2% as well. The estimated maximum application rate, based on the rate for wheat, was used.

[a] The minimum PPE for loaders is long sleeve shirt, long pants, shoes and socks, eye protection, and chemical resistant gloves.(Note: the label does not specify long sleeves or long pants).

The minimum PPE for applicators is long sleeve shirt, long pants, chemical resistant gloves, and shoes with socks.

[b] UE = Dermal Unit Exposure is the amount of exposure measured in terms of mg ai/lb a.i handled (source: PHED v.1.1; or Kurtz and Bode, 3a & 3b only).

[c] ADD(mg/kg/day)[dermal]: = unit exposure (UE) from PHED in mg/lb ai handled * lb ai/day * 0.03 (dermal absorption)/ [60 kg (short-term) or 70 kg (intermediate-term) body weight].

[d] MOE = NOAEL/ADD; Short-term NOAEL dermal and inhalation = 1.0 mg/kg bw; Intermediate or Long-term NOAEL = 0.1 mg/kg bw

[e] UE = Unit Exposure for inhalation is expressed in terms mg ai/lb ai handled.

[f] ADD(mg/kg/day) [inhalation] = unit exposure (UE) from PHED in mg/lb ai handled * lb ai/day/ [60 kg (short-term) or 70 kg (intermediate-term) body weight].

[g] MOE Total = NOAEL/ (ADD [dermal] + ADD [inhalation]); the ADDs may be added as endpoint are based on a common NOAEL

Table 11. Occupational Handler Short- and Intermediate-Term Exposure Estimate and Risk Assessment Summary for Chlorpyrifos-methyl: Maximum Personal Protective Equipment (PPE)

		DERMAL					INHALATION					Combined MOE	
		(With Maximum PPE)[a]					(With Respirator)					Max. PPE	
Application Scenario	(lb ai/ day)*	UE[b] (mg/lb ai)	ADD[c] (mg/kg/day)		ST MOE[d] NOAEL = 1 mg/kg	Int. MOE[d] NOAEL = 0.1 mg/kg	UE[e] (mg/lb ai)	ADD[f] (mg/kg/day)		ST MOE[d] NOAEL= 1 mg/kg	Int. MOE[d] NOAEL = 0.1 mg/kg	MOE Total[g]	
			Short-term	Inter.-term				Short-term	Inter.-term			Short Term	Inter. Term
Mixer/Loader													
Open Loading Dusts [Wettable Powder] for Automated Application Systems (1)	24	0.132	1.6 E-3	1.4 E-3	620	71	8.7 E-3	3.5 E-3	3.0 E-3	290	33	200	23
Mixing/Loading Liquids for Automated Application (2)	29	0.017	2.5 E-4	2.1 E-4	4000	480	2.4 E-4	1.2 E-4	9.9 E-5	8300	1000	2700	320
Mixer/Loader/Applicator													
3a)Treating Grain in Truck or (b)Top-Dressing Grain with Dust by Hand-Pump	3	143	0.21	0.18	4.7	0.54	No Data						
	0.66		0.47	0.040	21	2.5							
4a)Treating Grain in Truck or b) Top-Dressing Grain with Dust by Power Duster	Unk.	No Data											
Backpack Spraying (5)	2	1.6	1.6 E-3	1.4 E-3	620	71	0.006	2.0 E-4	1.7 E-4	5000	590	560	64
High Pressure Handwand Sprayer (6)	3.3	1.6	2.6 E-3	2.3 E-3	380	44	0.024	1.3 E-3	1.1 E-3	770	91	260	29

* There are two strengths of dust, but the 3% was selected for calculations as they will be more conservative and thus suffice for 2% as well. The estimated maximum application rate, based on the rate for wheat, was used.

[a] The maximum dermal PPE for loaders and applicators is coveralls over long sleeve shirt, long pants and shoes with socks, eye protection, chemical resistant gloves.

[b] UE = Dermal Unit Exposure is the amount of exposure measured in terms of mg ai/lb a.i handled; 50% body protection factor for coveralls (source: PHED v.1.1; or Kurtz and Bode, 3a & 3b only).

[c] ADD(mg/kg/day)[dermal]: = unit exposure (UE) from PHED in mg/lb ai handled * lb ai/day * 0.03 (3% dermal absorption)/ [60 kg (short-term) or 70 kg (intermediate-term) body weight].

[d] MOE = NOAEL/ADD; Short-term NOAEL dermal and inhalation = 1.0 mg/kg bw; Intermediate or Long-term NOAEL = 0.1 mg/kg bw

[e] UE = Unit Exposure for inhalation is expressed in terms mg ai/lb ai handled.; 80% protection factor for dust/mist respirator use

[f] ADD(mg/kg/day) [inhalation] = unit exposure (UE) from PHED in mg/lb ai handled * lb ai/day * 100% absorption/ [60 kg (short-term) or 70 kg (intermediate-term) body weight].

[g] MOE Total = NOAEL/(ADD [dermal] + ADD [inhalation]); the ADDs may be added as the endpoints are based on a common NOAEL

Table 12. Chlorpyrifos-methyl: Summary of Combined Dermal and Inhalation MOEs

Scenario	Minimum PPE (Single Layer, Gloves)		Maximum PPE (Coveralls + Respirator)	
	Short-Term	Intermediate-Term	Short-Term	Intermediate-Term
Mixer/Loader				
Loading Dust (1)	53	6.0	200	23
Mixing/Loading Liquid (2)	1100	130	2700	320
Mixer/Loader/Applicator				
Hand-Held Duster	3.3 [dermal]	0.39 [dermal]	4.7 [dermal]	0.54 [dermal]
(4a) Treating Grain in Truck (4b) Top-Dressing Grain	15 [dermal]	1.6 [dermal]	21 [dermal]	2.5 [dermal]
Power Duster (5)	ND	ND	ND	ND
Backpack Spraying (6)	290	34	560	64
MLAP High Pressure Handwand Sprayer (7)	93	11	260	29

ND = No Data
MLAP = Mixer/Loader/Applicator
MOE > 100 do not exceed HED's level of concern

3 Aggregate Risk Estimates and Risk Characterization

Based on the use pattern, an aggregate risk estimate is not required as drinking water and residential exposures to chlorpyrifos-methyl are not anticipated.

4 Cumulative Exposure and Risk

EPA has determined that chlorpyrifos-methyl has a common mechanism of toxicity with other members of the organophosphates. However, the Agency is in the process of developing methodology to conduct a cumulative risk assessment. For this risk assessment, therefore, EPA has not conducted a cumulative risk assessment.

5 Endocrine Disruptor Effects

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR 71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of chlorpyrifos-methyl and its end-use products for endocrine effects may be required.

6 Data Needs

Currently there are data gaps for the following studies. Inclusion of the study as a data gap below indicates that there is currently no acceptable study for the listed study type.

(860.1340)	Residue Analytical method
(860.1380)	Storage Stability
(860.1500)	Magnitude of the Residue study
(860.1520)	Processed Food/Feed
(870.1100)	Acute oral toxicity-Rat
(870.1200)	Acute dermal toxicity -Rabbit
(870.1300)	Acute inhalation study- Rat
(870.2400)	Primary ocular irritation-Rabbit
(870.2500)	Primary dermal irritation-Rabbit
(870.2600)	Dermal sensitization study- Guinea pigs
(870.6100)	Delayed neurotoxicity study - Hens
(870.6200)	Acute neurotoxicity study - Rat
(870.3200)	Subchronic dermal toxicity study - Rat or Rabbit
(870.3465)	Subchronic inhalation study -Rat
(870.6200)	Subchronic neurotoxicity study -Rat
(870.4100)	Chronic toxicity-Dog
(870.3700)	Prenatal developmental neurotoxicity study - Rabbit
(870.3800)	Two-generation reproduction study - Rat
(870.6300)	Developmental neurotoxicity study -Rat
(870.7485)	General metabolism-Rat

(870.7600) Dermal absorption
(875.1100) Outdoor dermal exposure
(875.1200) Indoor dermal exposure
(875.1300) Outdoor inhalation exposure
(875.1400) Indoor inhalation exposure
(875.1500) Biological monitoring

7 Attachments

A. Toxicology Endpoint Selection - Report of the Hazard Identification Assessment Review Committee, 5/17/99

B. Toxicology Section of the RED Chapter, 4/17/00

C. FQPA Safety Factor Recommendations for the Organophosphates, 8/6/98.

D. Chlorpyrifos-Methyl: Revised Acute and Chronic Dietary Exposure Analyses. 10/28/99.

E. Revised Chlorpyrifos Methyl: Residue Chemistry Chapter of the RED, 11/1/99.

F. HED Occupational and Residential Exposure Chapter, Revised 4/17/00.

G. Review of Chlorpyrifos-methyl Incident Reports, 4/15/99.

ATTACHMENTS